

SARS COV2 & THE HEART

COVID-19 & THE HEART

OBJECTIVES

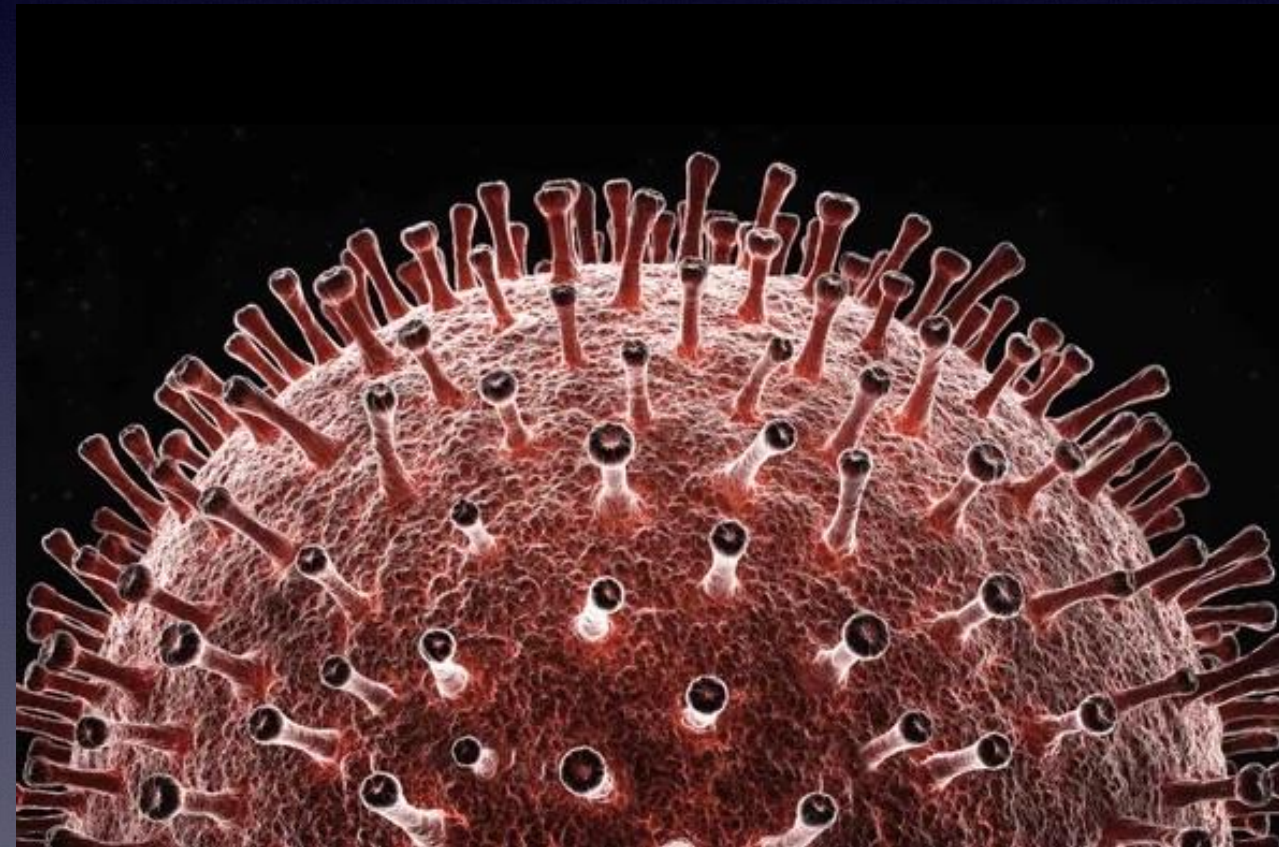
- Provide a Reference to the Origin of SARS COV2 (COVID-19)
- Brief BackGround of the current Pandemic
- Types of Viruses
- Viral Pathogenesis
- SARS COV2 Mechanism of Infection
- Consequences of Infection
- Therapy

The origin of SARS-CoV-2

- It has been determined that severe acute respiratory syndrome due to covid 19 is derived from bat coronaviruses.
- It is estimated that there are at least 3200 coronaviruses that infect bats.
- www.thelancet.com/infection Vol 20 August 2020

SARs-CoV2

In late December, 2019, a cluster of cases of viral pneumonia was linked to a seafood market in Wuhan (Hubei, China), and was later determined to be caused by a novel coronavirus.



SARS COV2

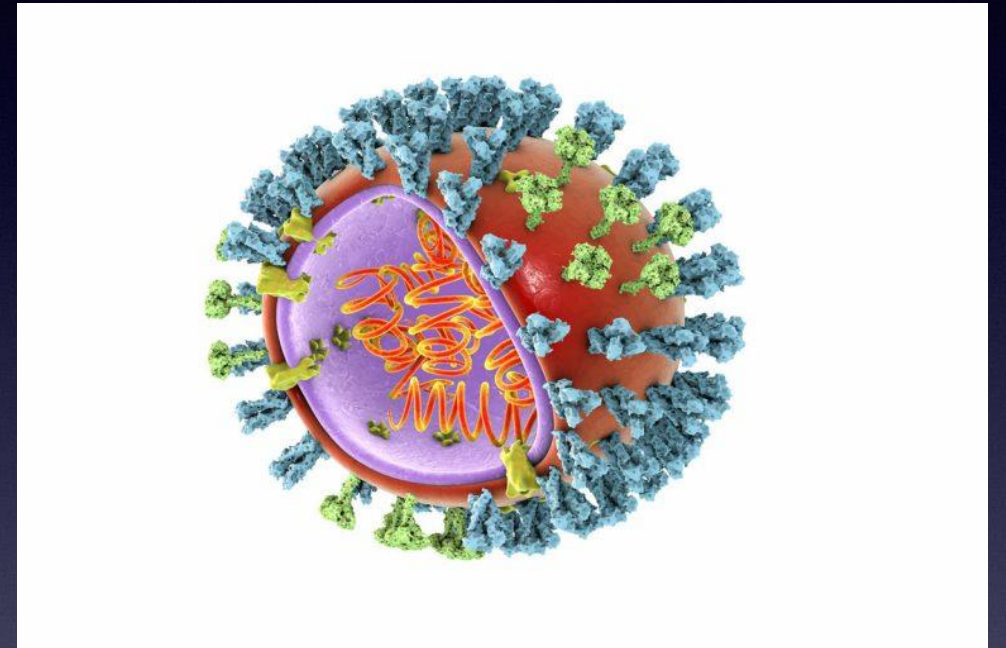
“A Novel Coronavirus”

- This novel virus has been named “**Severe Acute Respiratory Syndrome Coronavirus 2**” (SARS-CoV-2) and the disease it causes has been named “**Coronavirus Disease 2019**” (COVID-19).
- On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and declared a national emergency in response to COVID-19.
- In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.

- Human coronaviruses were first identified in the mid-1960s. The seven coronaviruses that can infect people are:
 - Common human coronaviruses
 - 229E (alpha coronavirus)
 - NL63 (alpha coronavirus)
 - OC43 (beta coronavirus)
 - HKU1 (beta coronavirus)
 - *Other human coronaviruses*
 - MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS)
 - SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS)
 - SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19)

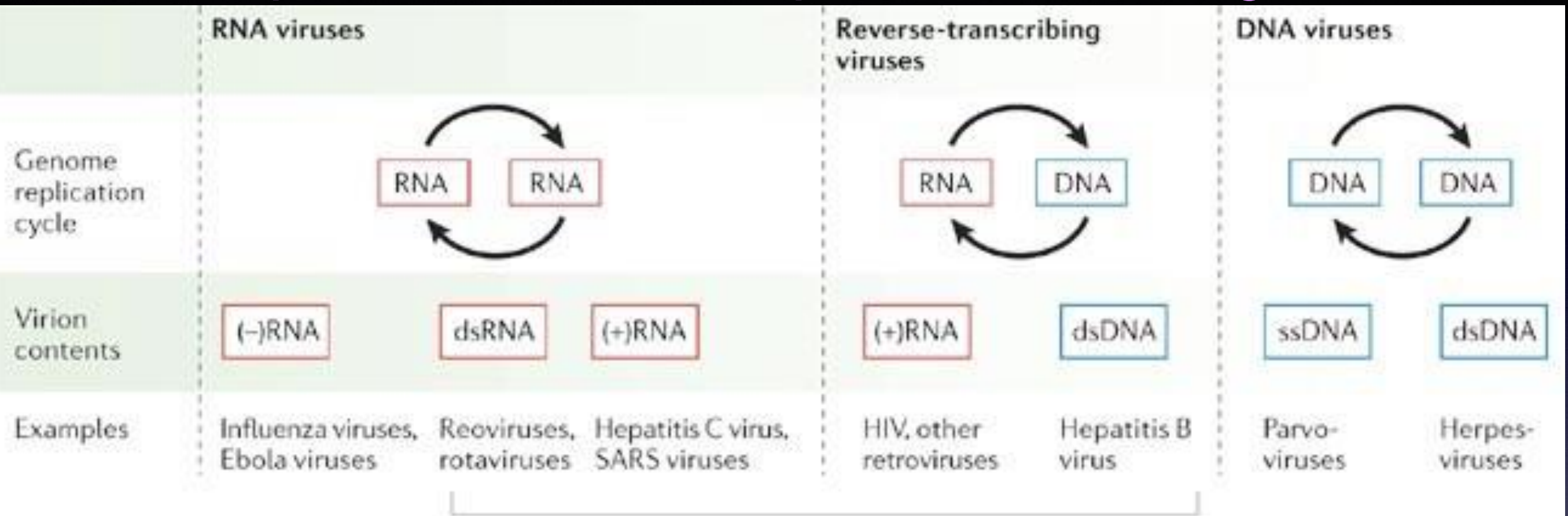
SARs-CoV2

- Enveloped
- Non-segmented
- RNA Virus
- Positive sense



Positive-sense viral RNA is similar to mRNA and thus can be immediately translated by the host cell. Negative-sense viral RNA is complementary to mRNA and thus must be converted to positive-sense RNA by an RNA polymerase before translation. ...

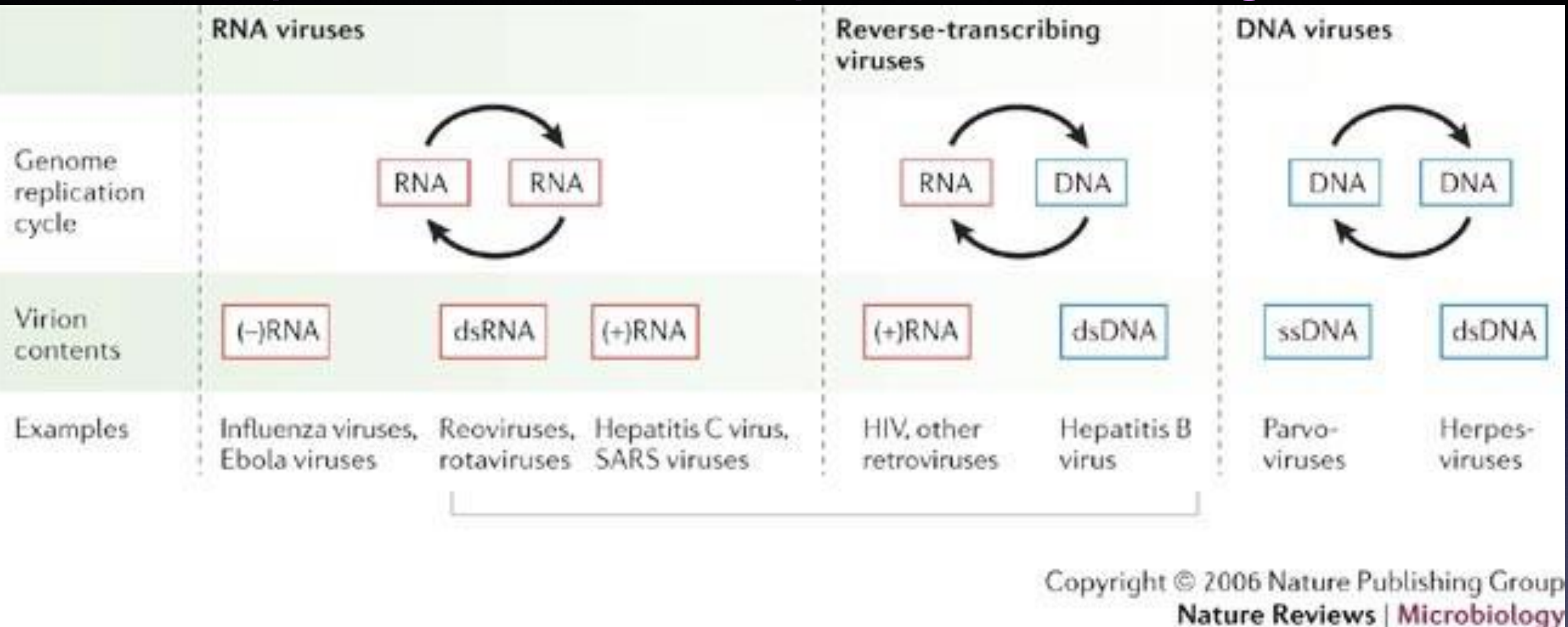
Seven classes of virus distinguished by genome replication and encapsidation strategies.



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Nature Reviews | Microbiology

Positive-sense viral RNA is similar to mRNA and thus can be immediately translated by the host cell. **Negative-sense viral RNA** is complementary to mRNA and thus must be converted to **positive-sense RNA** by an **RNA polymerase** before translation. ...

Seven classes of virus distinguished by genome replication and encapsidation strategies.



Reverse-transcribing RNA viruses, such as retroviruses, use the enzyme to **reverse-transcribe** their RNA genomes into DNA, which is then integrated into the host genome and replicated along with it.

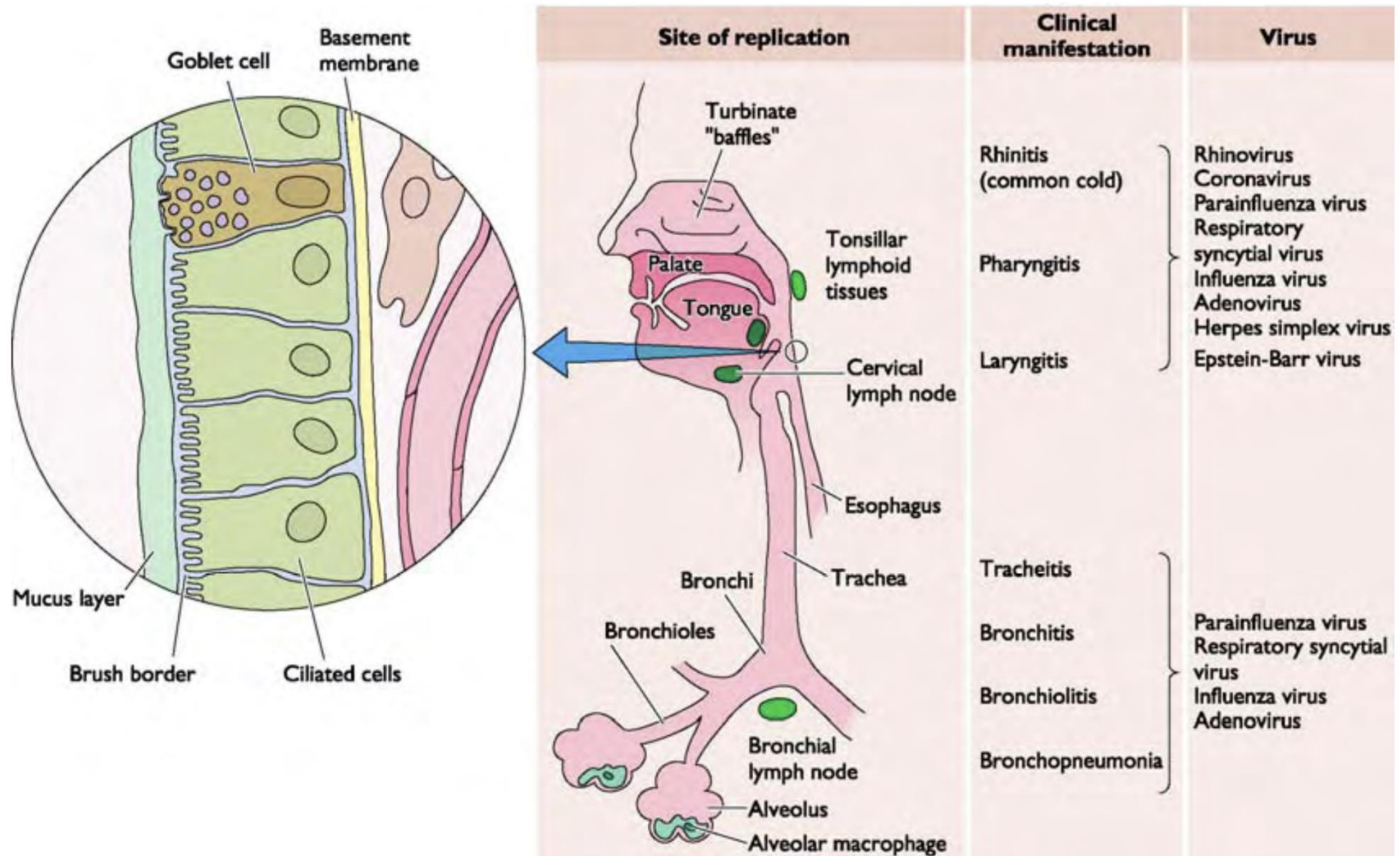


Figure 2. Sites of viral entry in the respiratory tract.

Viruses may enter the respiratory tract in the form of aerosolized droplets expelled by an infected individual by coughing or sneezing, or through contact with saliva from an infected individual. Larger virus-containing droplets are deposited in the nose, while smaller droplets find their way into the airways or the alveoli. To infect the respiratory tract successfully, viruses must not be swept away by mucus, neutralized by antibody, or destroyed by alveolar macrophages.

1
nose
throat



ACE2



2
lungs

ACE2

ACE2

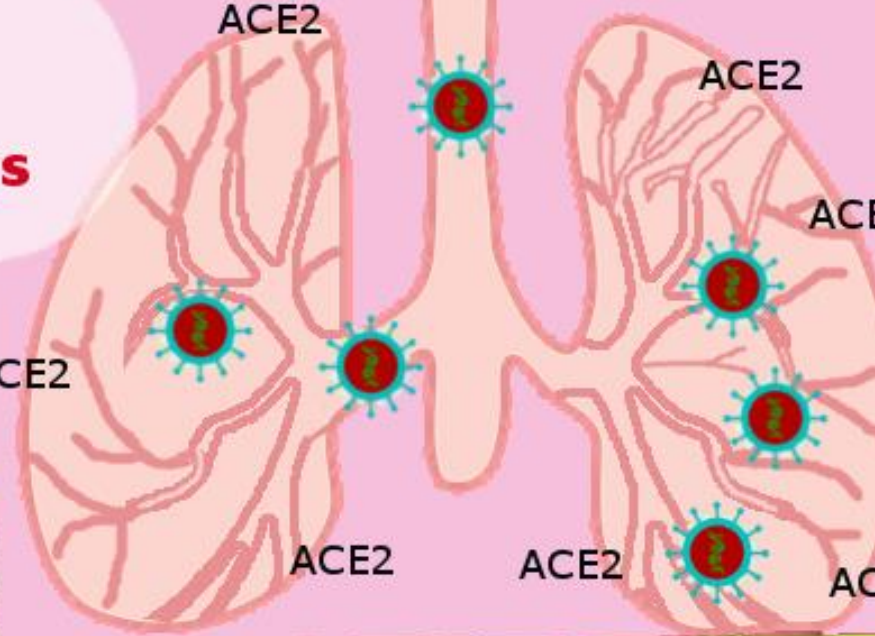
ACE2

ACE2

ACE2

ACE2

ACE2



Clinical factors



Timing

- Incubation: ~5d after exposure (range 2-14d)
- Symptoms: ~12d after exposure (range 8-16d, or never)
- Infectiousness: before onset of symptoms
- Seroconversion: ~5-10d after symptom onset
- Diagnosis of infection: typically after onset of symptoms

Viral Concentrations ^{*,*,*}

- Nasal (10^{6-9} RNA/swab)
- Throat (10^{4-8} RNA/swab)
- Sputum (10^{6-11} RNA/mL)
- Stool (10^{4-8} RNA/g)
- Blood (low levels)
- Urine (not detectable?)

Variables Affecting Disease Severity ^{*,*}

- Sex (♂ > ♀)
- Age (Old > Young)
- Cardiovascular diseases, cancer, respiratory diseases, diabetes, others

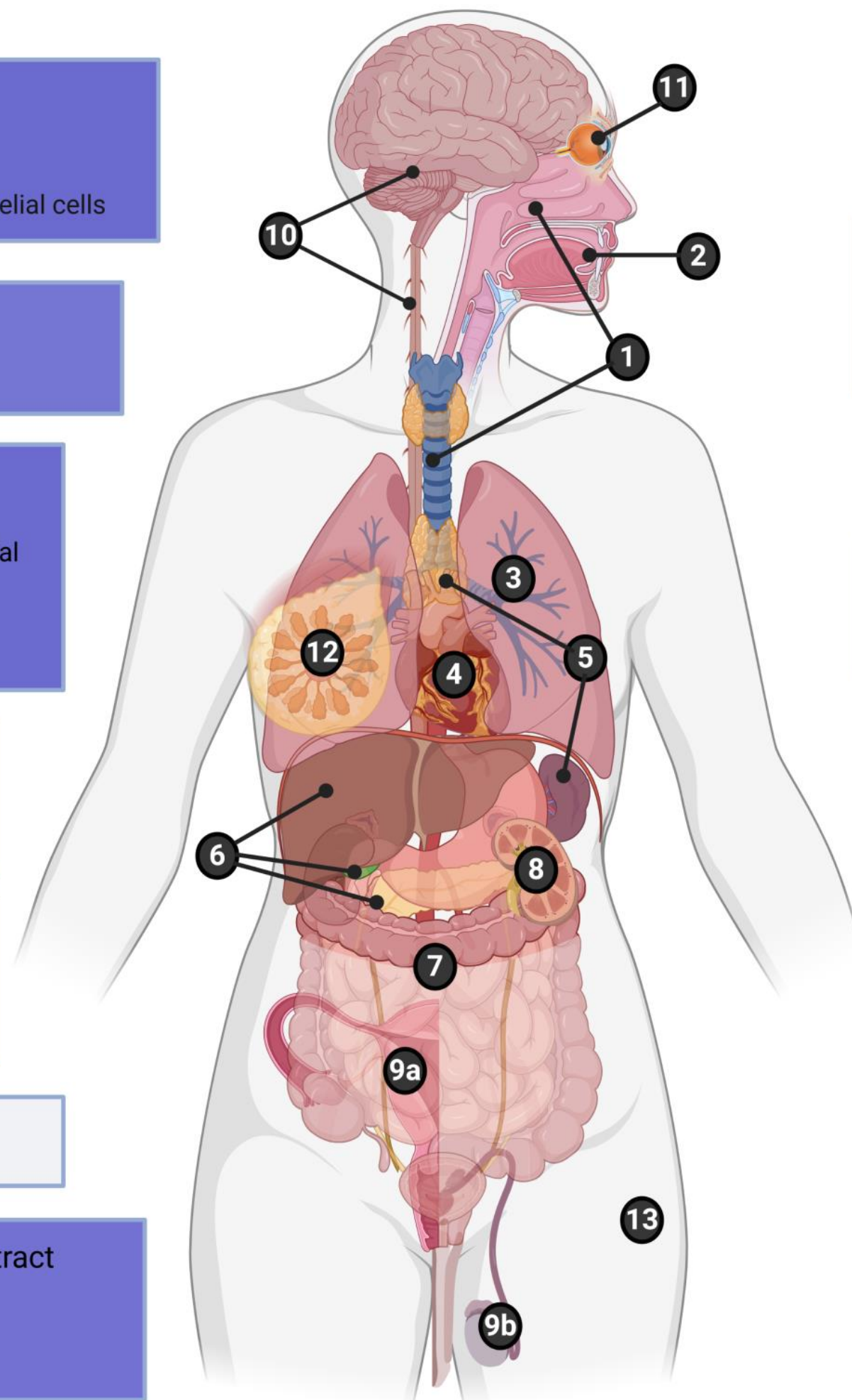
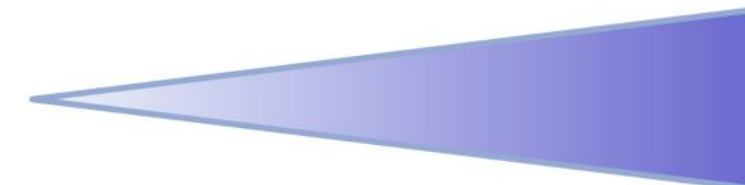
Impact

- Confirmed cases, outcomes, simulators, others: JHU Covid Center; MGH Simulator; Our World In Data; DIVOC

SARS-CoV-2

low

high



1. Upper airways

Mucus
Nasopharynx
Trachea ciliated epithelial cells

2. Mouth

Sputum
Oropharynx

3. Lungs

Bronchoalveolar lavage
Ciliated and secretory epithelial cells
Type I and II pneumocytes
Alveolar macrophages

4. Cardiovascular system

Heart interstitial fibroblasts
Vessel endothelial cells

5. Immune system

Blood
Lymph nodes
Spleen

6. Liver, gallbladder and pancreas

7. Gastrointestinal tract

Stool
Stomach
Enterocytes

8. Urinary system

Urine
Kidney tubular epithelial cells and podocytes

9a. Female reproductive tract

9b. Male reproductive tract

Testicular spermatogenic, Sertoli and Leydig cells

10. Nervous system

Brain
Cerebrospinal fluid

11. Eye

Tears
Conjunctiva

12. Mammary glands

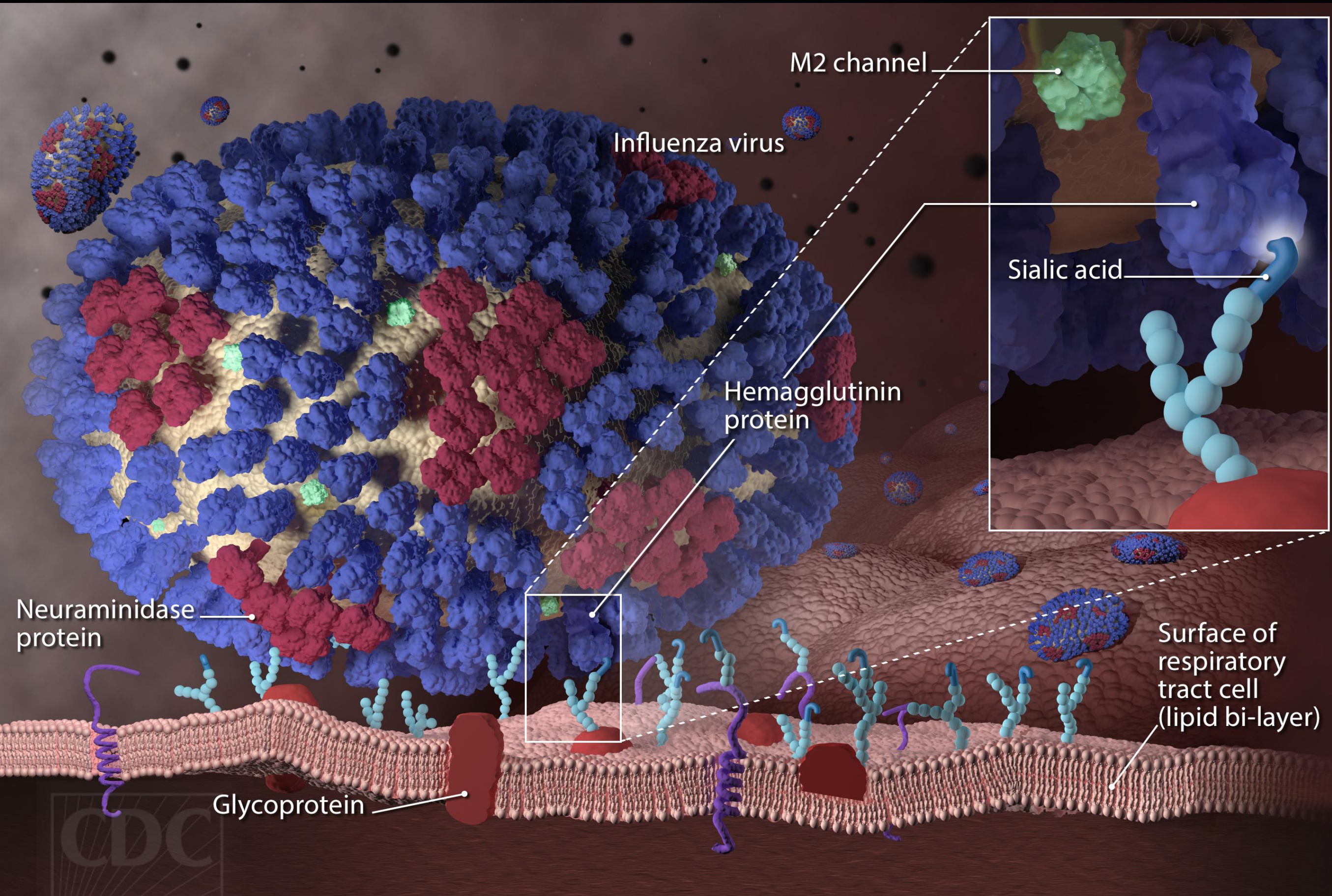
Breast milk

13. Skin and adipose tissue

Viral Pathogenesis

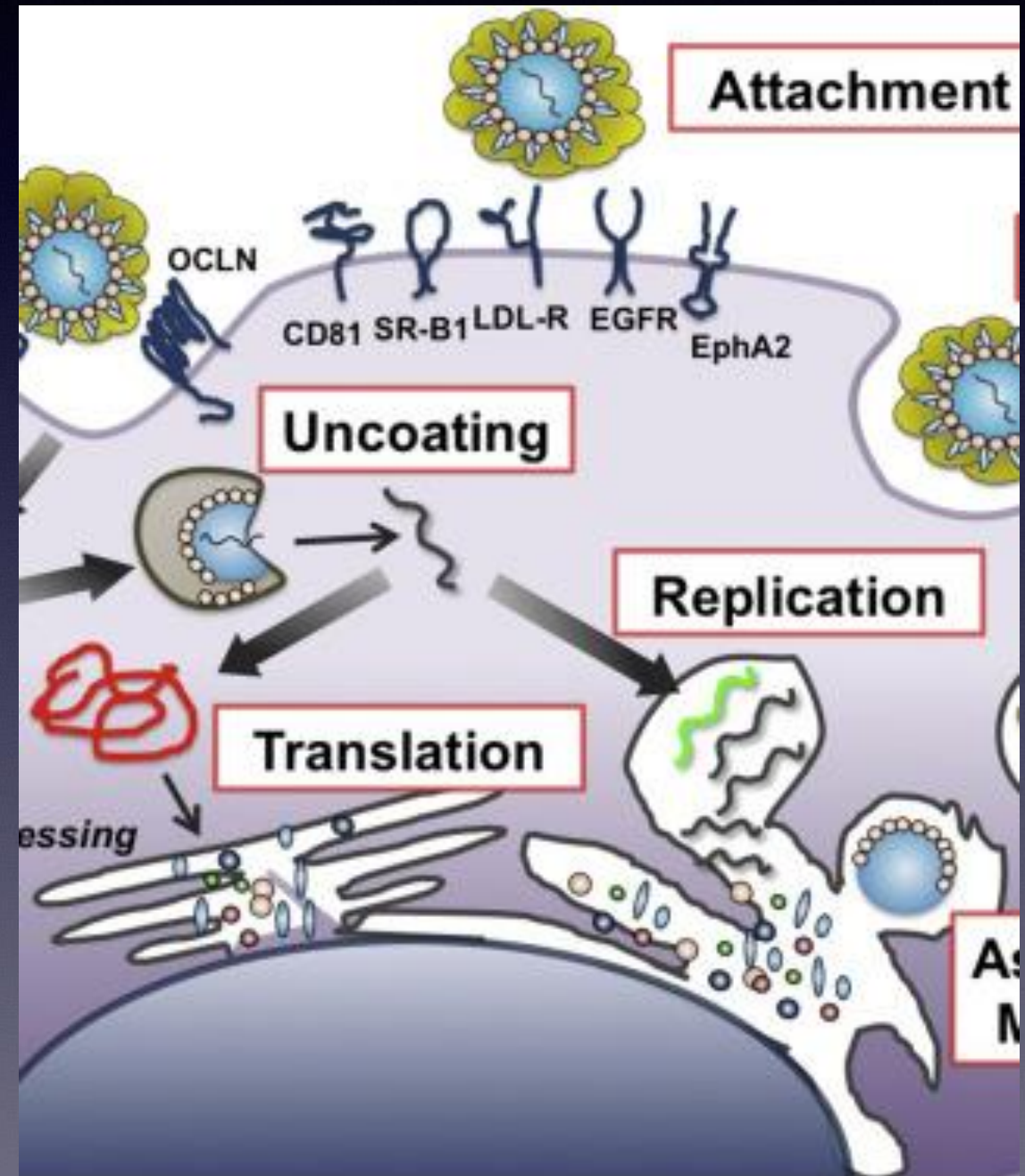
Entire process by which viruses cause disease

- Viral disease is a sum of the effects on the host
- Of virus replication
- Of the immune response.

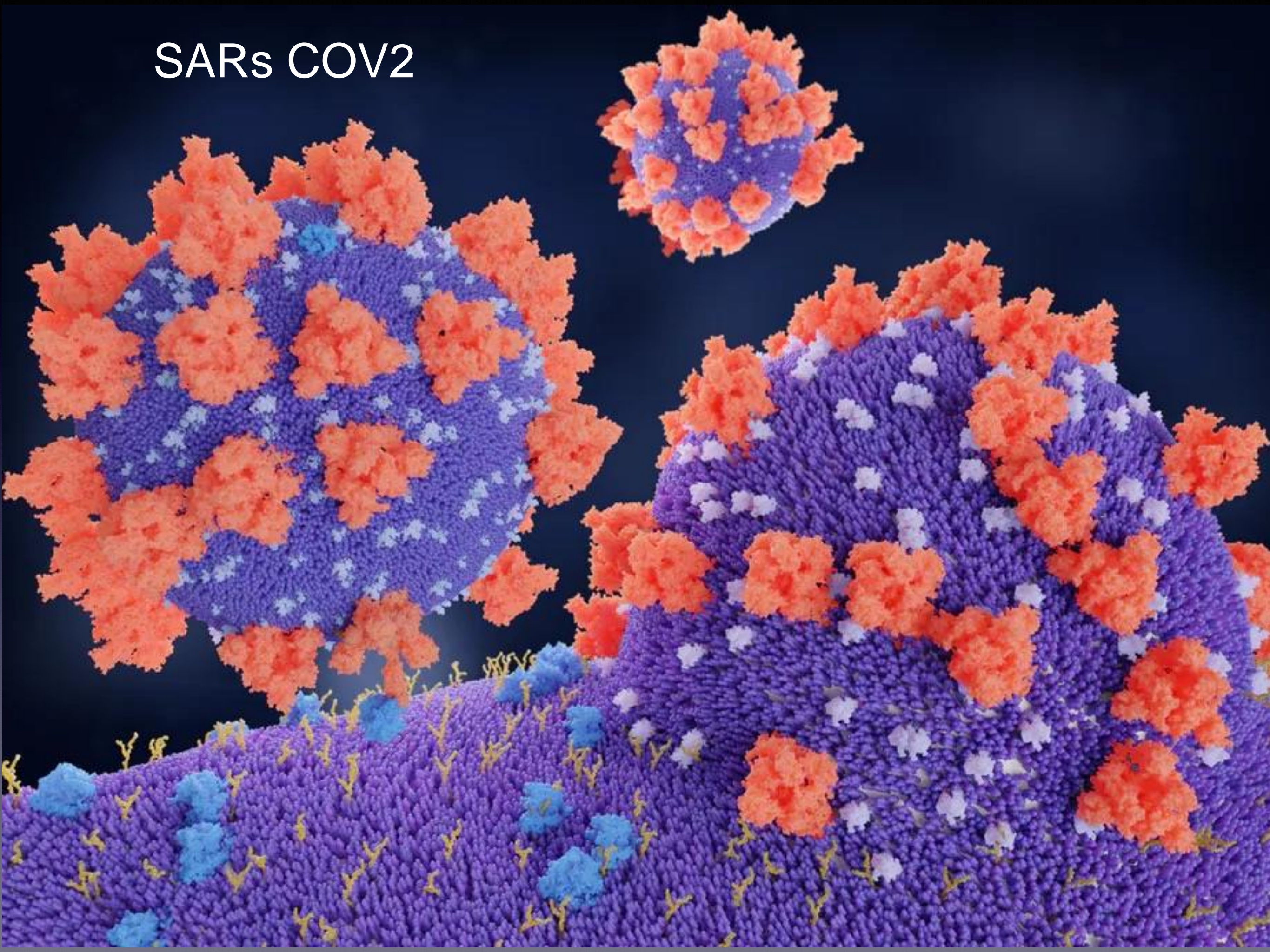


HCV virion circulates in the bloodstream either as a free particle or surrounded by host low-density lipoproteins; then, attaches onto the target cell

Attaches onto the target cell membrane by sequential binding of various receptor molecules, and enters into the cell by a clathrin-mediated endocytosis process.

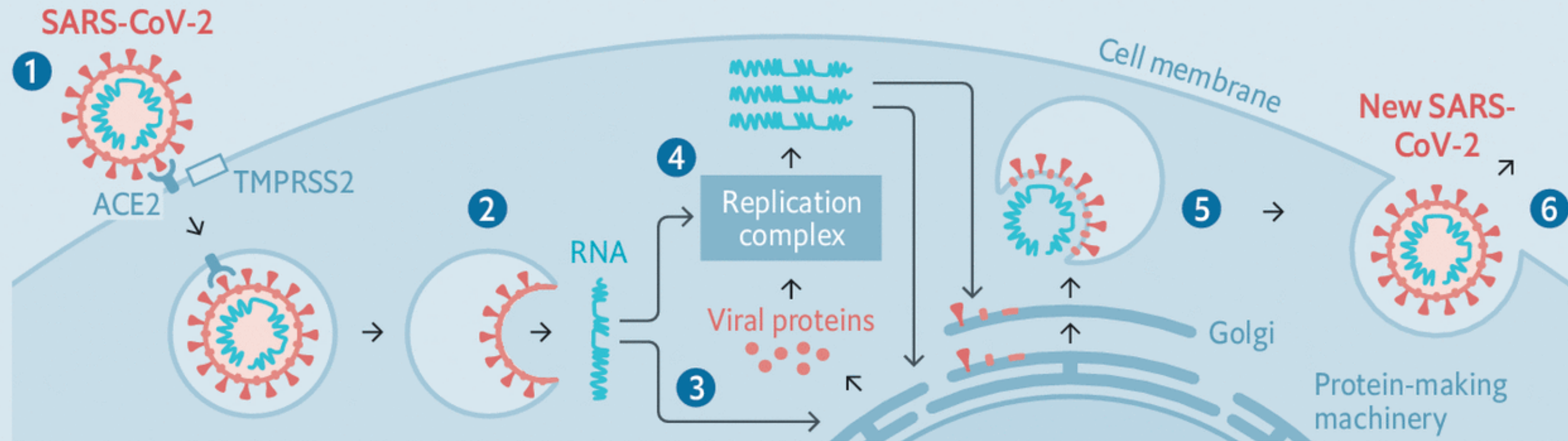


SARs COV2



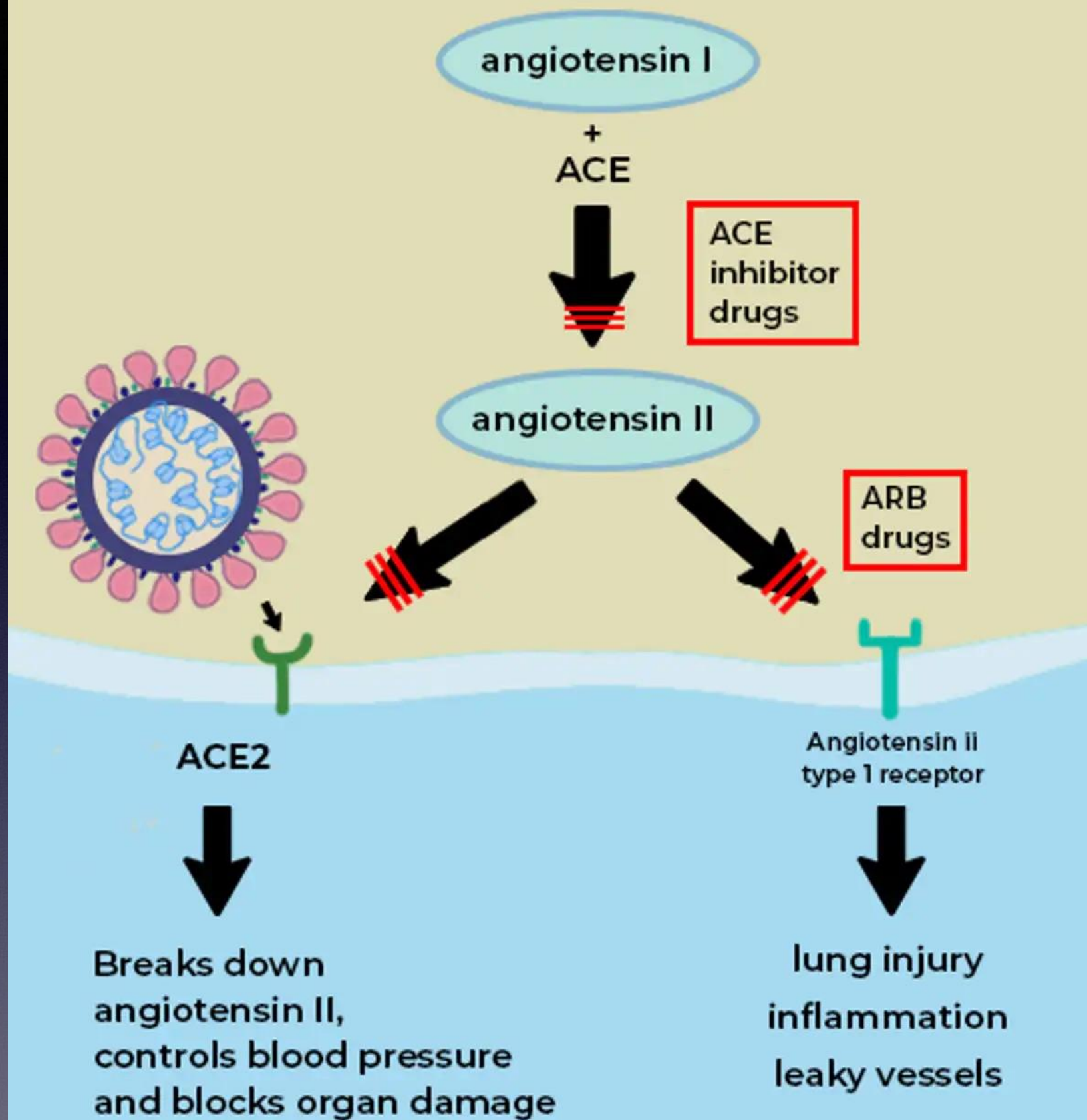
Hijack

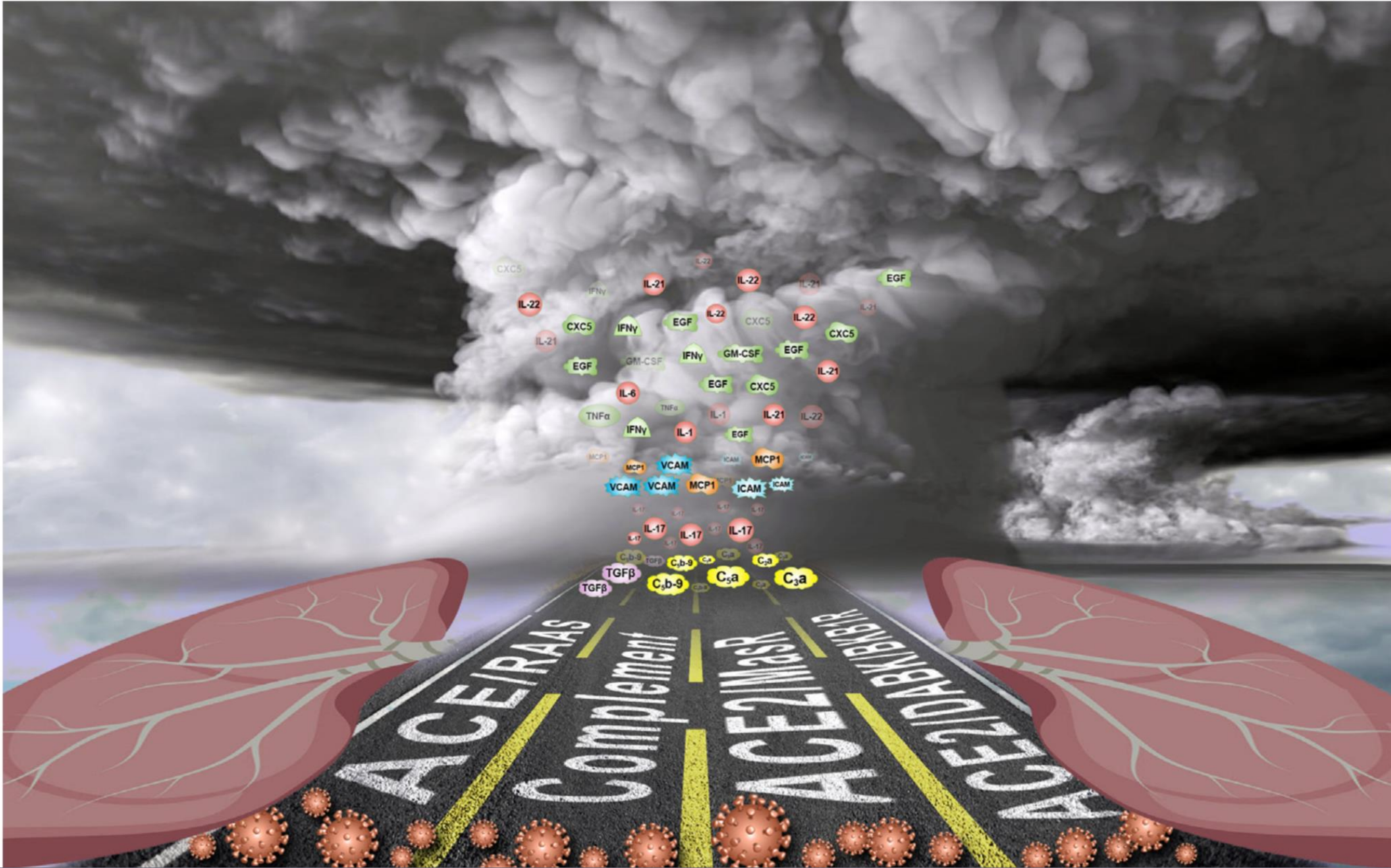
How SARS-CoV-2 replicates itself in the cells of those infected



1 Spike protein on the virion binds to ACE2, a cell-surface protein. TMPRSS2, an enzyme, helps the virion enter **2** The virion releases its RNA **3** Some RNA is translated into proteins by the cell's machinery **4** Some of these proteins form a replication complex to make more RNA **5** Proteins and RNA are assembled into a new virion in the Golgi and **6** released

Sources: Song et al., *Viruses*, 2019; Jiang et al., *Emerging Microbes and Infections*, 2012; *The Economist*





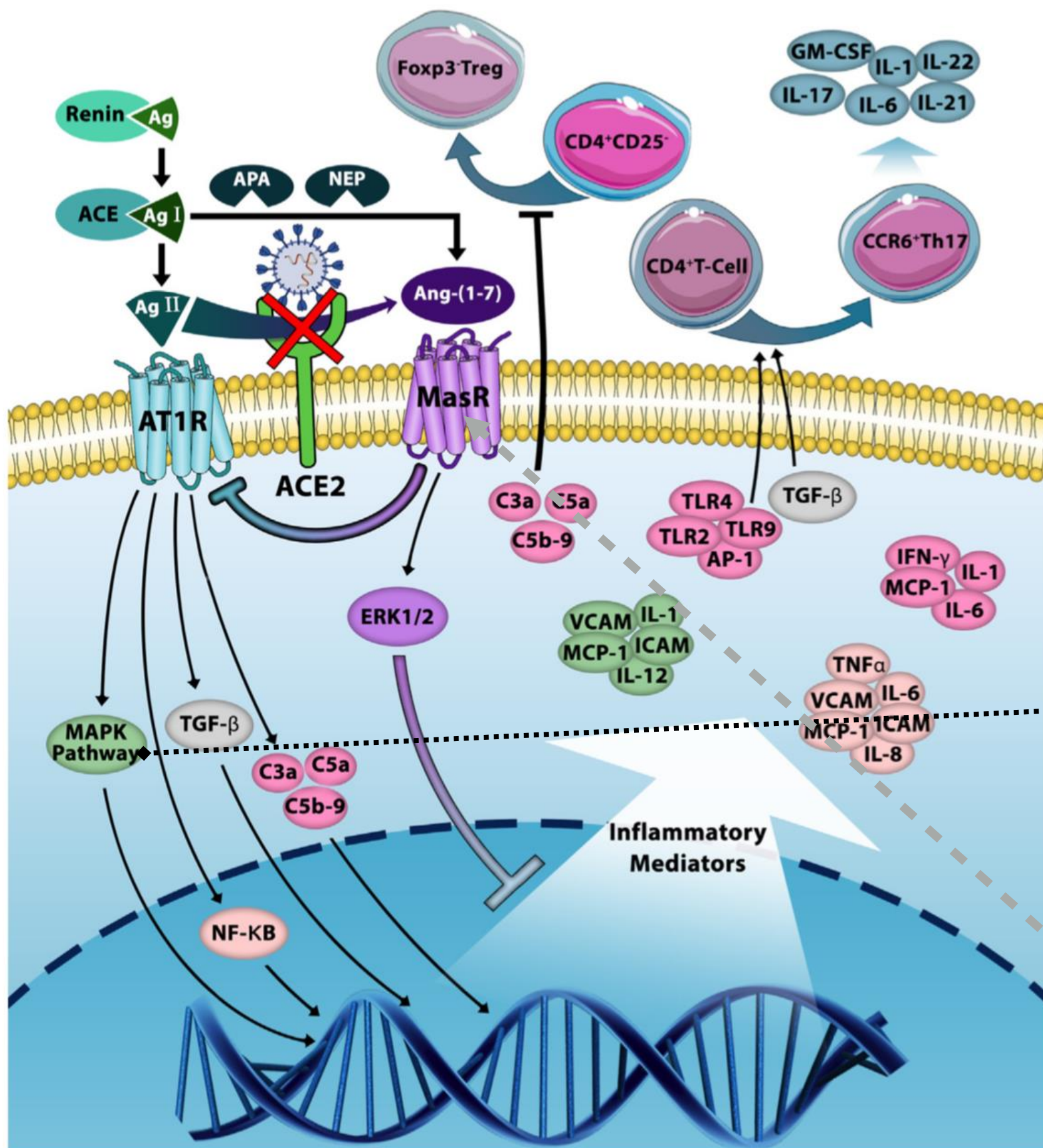


Fig. 2. ACE/Angiotensin II/AT1R and ACE2/MasR axis. The SARS-CoV-2 induced imbalance of ACE2/ACE that results in AT1R-mediated inflammatory response which will be accompanied with activation of the complement system, MAPK and NF-κB. The decrement of Ang (1–7) following SARS-CoV-2-mediated ACE2 down-regulation results in attenuation of MasR function. The MasR modulates AT1R-mediated inflammatory cytokine responses. Ang-(1–7) modulates the activity of ERK 1/2 via MasR. ERK 1/2 pathway induces production of IL-10, as an anti-inflammatory cytokine. Ang II, TLR2, TLR4, TLR9, and AP-1 transcription factor induce TGF-β expression. TGF-β has a role in the differentiation of T helper 17 cells from naive CD4+ T-cells.

**The p38 MAPK Pathway
Crucial Role in the
Release of Pro-
inflammatory Cytokines**

**GPCR (G-protein-
coupled receptor)
through which Ang
(angiotensin)-(1–7)
signals.**

Preliminary predictive criteria for COVID-19 cytokine storm

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Stefania Gallucci ⁴, David Fleece,⁵ Michael Bromberg,⁶ Gerard J Criner,⁷ Temple
University COVID-19 Research Group

Table 4 Predictive criteria for COVID-19 cytokine storm

Entry criteria (must be all met)	Cut-off values
+Signs/symptoms of COVID-19	
±RT-PCR positive for COVID-19	
+GGO by HRCT (or chest X-ray)	
Ferritin	>250 ng/mL
C reactive protein	>4.6 mg/dL
AND (one variable from each cluster)	
Cluster I	
Albumin	<2.8 g/dL
Lymphocytes (%)	<10.2
Neutrophil Abs	>11.4 K/mm ³
Cluster II	
ALT	>60 U/L
AST	>87 U/L
D-dimers	>4,930 ng/mL
LDH	>416 U/L
Troponin I	>1.09 ng/mL
Cluster III	
Anion gap	<6.8 mmol/L
Chloride	>106 mmol/L
Potassium	>4.9 mmol/L
BUN:creatinine ratio	>29 ratio

Criteria are met when patients fulfil all the entry criteria and at least one criterion per each cluster. Cut-off values were calculated using a genetic algorithm.

Abs, absolute numbers; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGO, ground-glass opacity; HTCT, high-resolution CT; LDH, lactate dehydrogenase; RT-PCR, reverse transcriptase PCR.

CYTOKINES

- Cytokines are a category of signaling molecules
- Cytokines mediate and regulate immunity, inflammation and hematopoiesis.
- Cytokines are a large group of proteins, peptides or glycoproteins
- Secreted by specific cells of immune system.

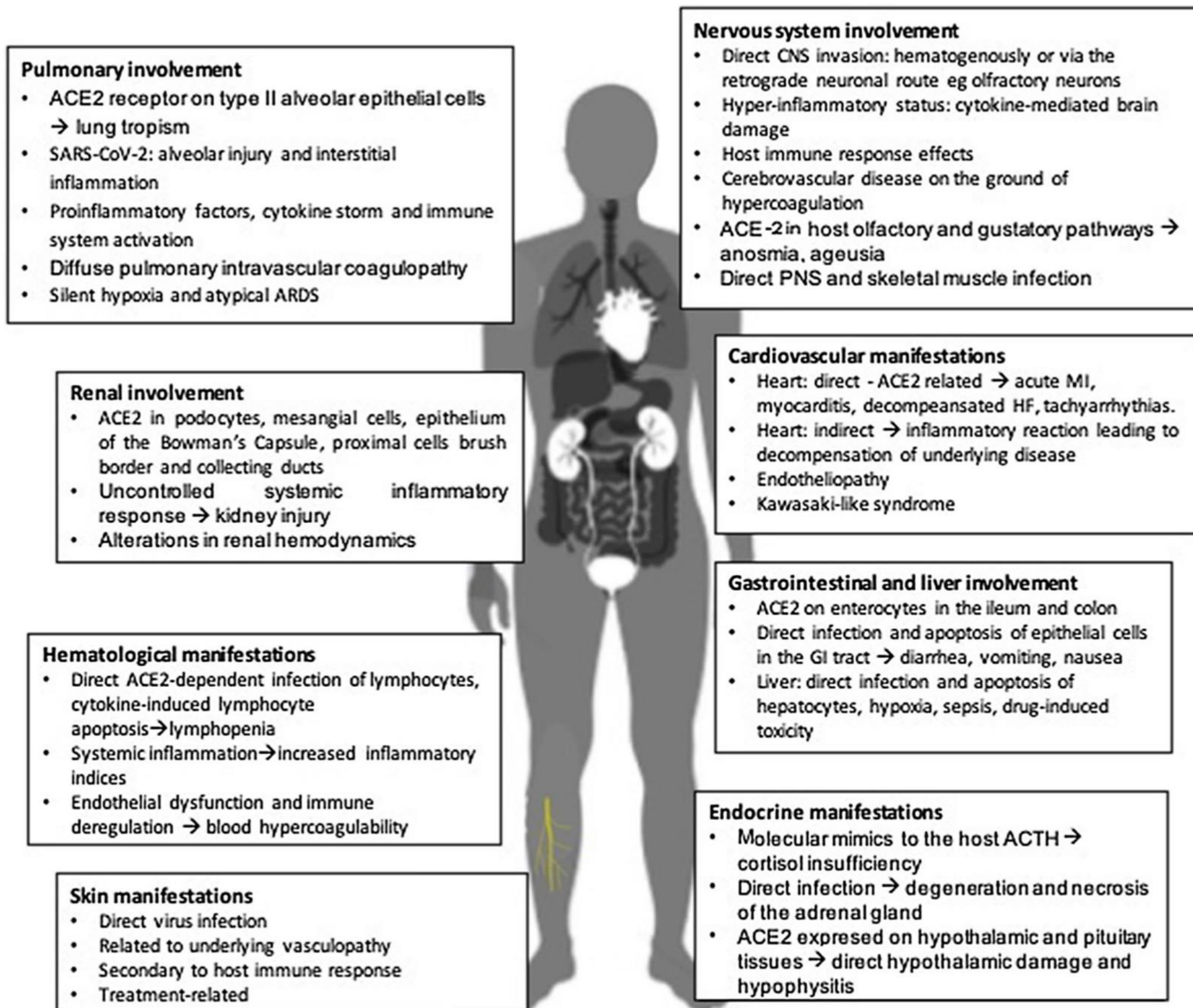


Fig. 1 Schematic overview of the systemic manifestations of COVID-19 infection and the underlying pathophysiology

Viral Spread

- Following replication at the site of entry, virus particles can remain localized, or can spread to other tissues
- Local spread of the infection in the epithelium occurs when newly released virus infects adjacent cells.
- These infections are usually contained by the physical constraints of the tissue and brought under control by the intrinsic and immune defenses.
- An infection that spreads beyond the primary site of infection is called disseminated.
- If many organs become infected, the infection is described as systemic.
- For an infection to spread beyond the primary site, physical and immune barriers must be breached.
- After crossing the epithelium, virus particles reach the basement membrane. The integrity of that structure may be compromised by epithelial cell destruction and inflammation.
- Below the basement membrane are sub-epithelial tissues, where the virus encounters tissue fluids, the lymphatic system, and phagocytes. All three play significant roles in clearing foreign particles, but also may disseminate infectious virus from the primary site of infection.

Table 1. Mechanisms of Myocardial Injury

	Hypothesized Mechanism of Injury
Myocarditis	Systemic inflammatory response; direct myocardial cell injury via viral entry using ACE-2 receptor; T-cell-mediated immune response
Myocardial infarction	Plaque rupture (Type I MI); myocardial oxygen supply/demand mismatch (Type II MI) from increased cardiometabolic demand
Microangiopathy/cytokine storm	Cytokine-induced activation of microvasculature predisposing to vasomotor abnormalities; augmented thrombosis and other aspects of dysfunction
Arrhythmia	Hypoxia-mediated; coronary perfusion impairment; direct tissue injury; scar-mediated injury, inflammatory response; medication-induced electrolyte abnormality
ACE indicates angiotensin-converting enzyme; and MI, myocardial infarction.	

Hypotension, tachycardia,
bradycardia, arrhythmia and
sudden cardiac death



ACE2

Surge of pro-
inflammatory cytokines &
systemic inflammatory
response syndrome

Primary Target

Cardiovascular disease
common in infected cohort &
may become rapidly unstable



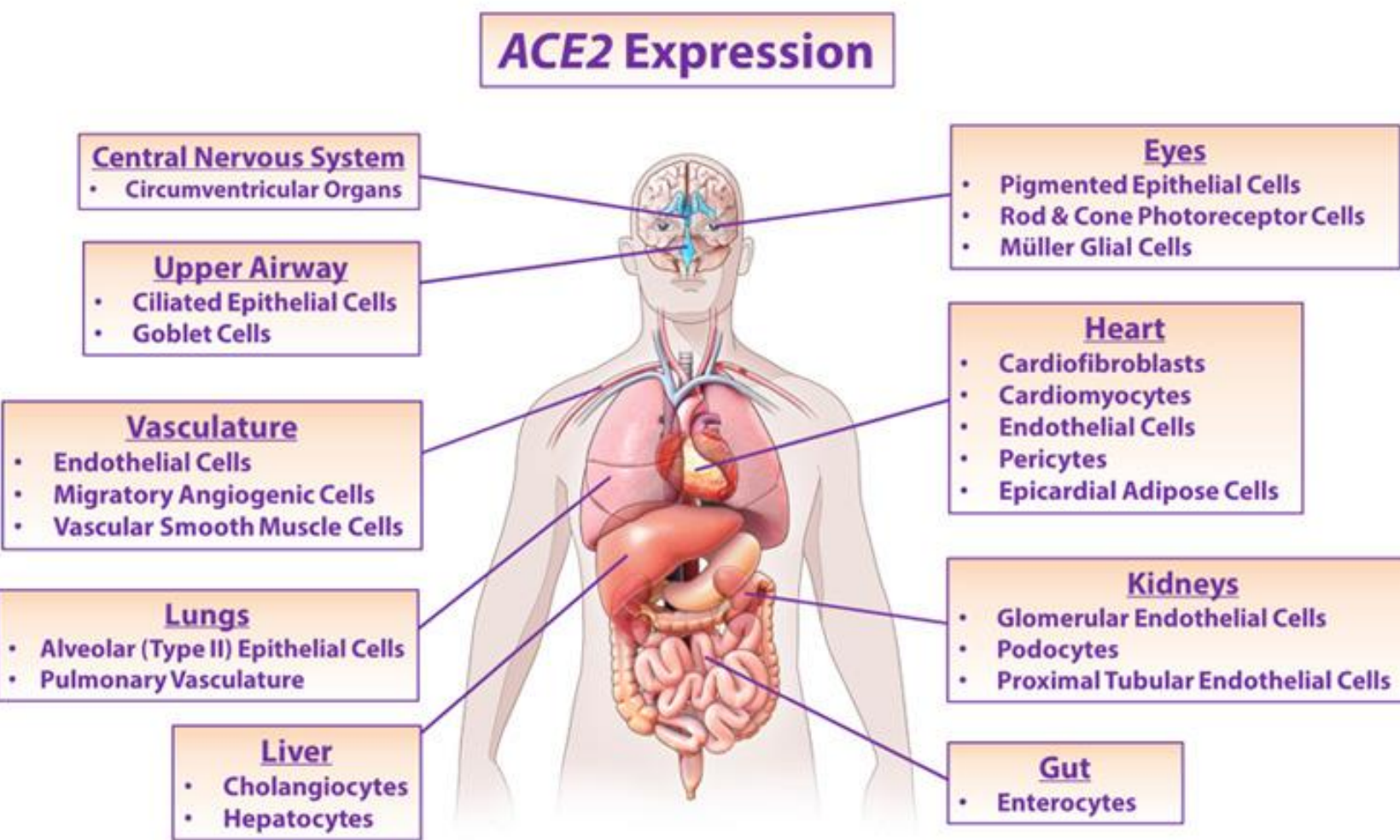
Increased severity of
respiratory syndrome
and higher risk of
adverse outcomes

↑ Metabolic demand

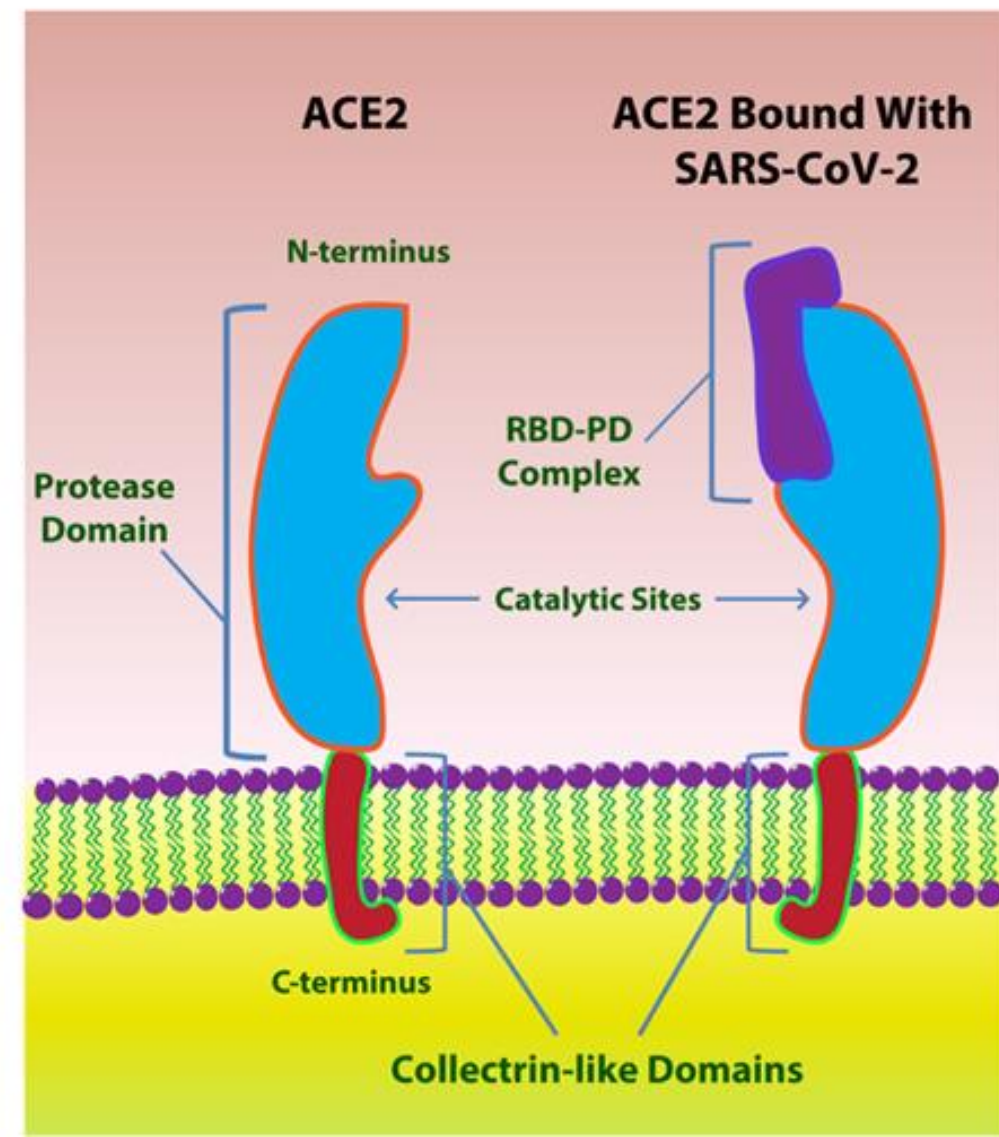
↓ Cardiac reserve

Significant Secondary Co-morbidity

A

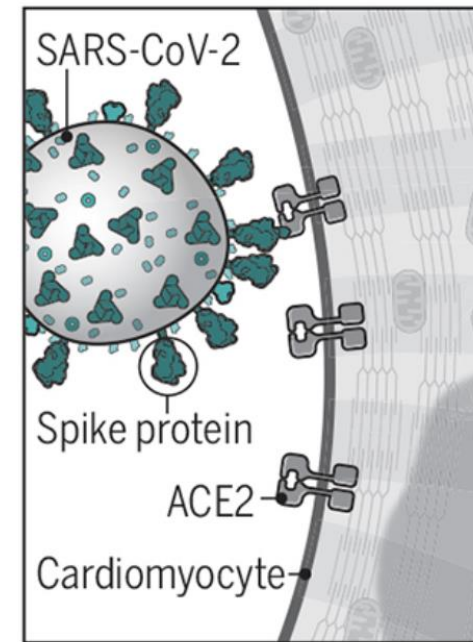
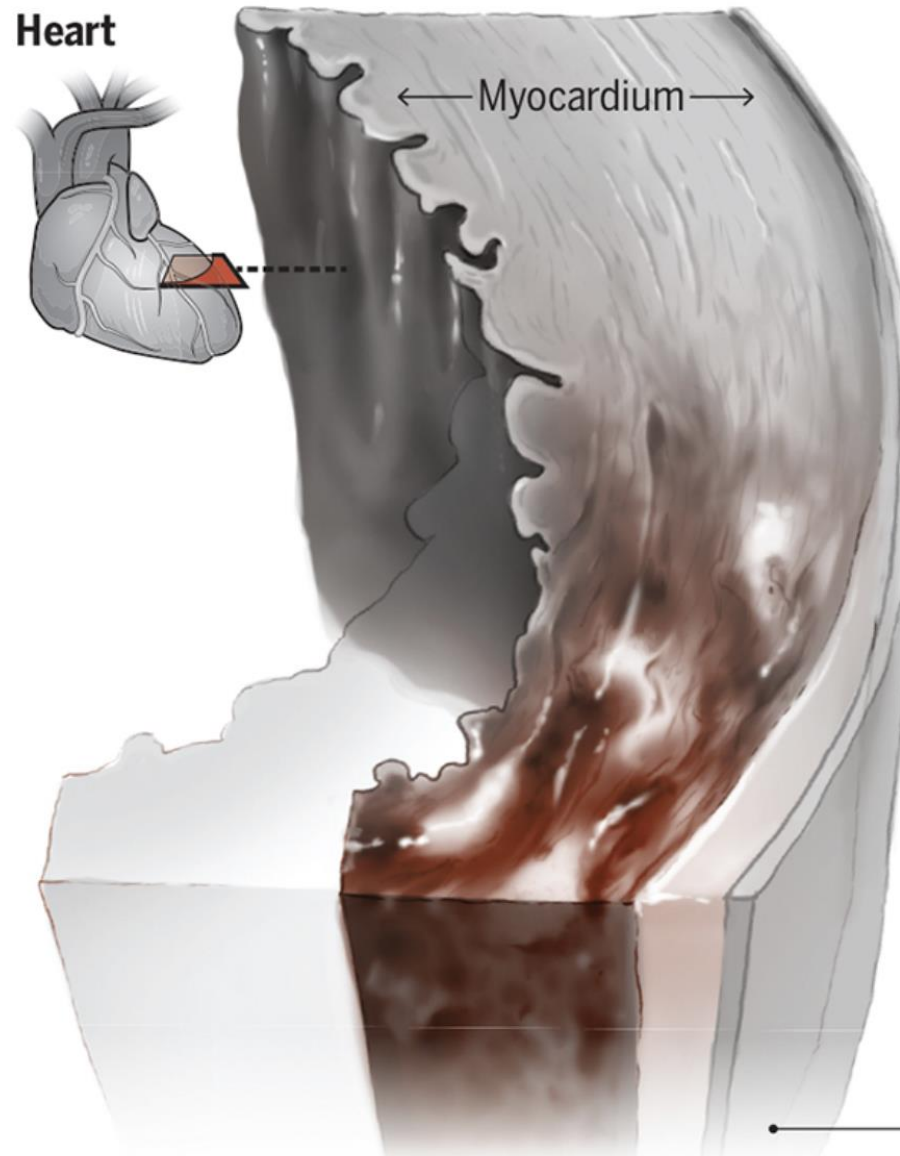


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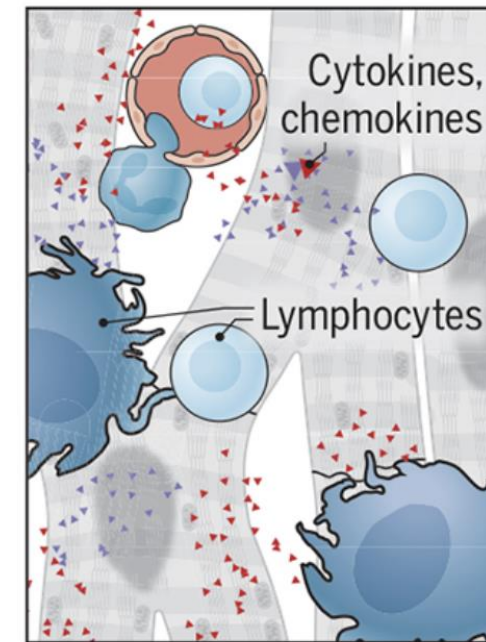


Damaging the heart

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has the potential to directly and indirectly induce cardiac damage.



SARS-CoV-2 can **directly infect** cardiomyocytes, attaching to angiotensin-converting enzyme 2 (ACE2) through its spike protein and entering the cells by fusing viral and cellular membranes.



SARS-CoV-2 infection can **indirectly damage** cardiomyocytes through systemic inflammatory responses and diminished blood supply (e.g., from blood clots and endothelitis, not shown).

◀ Complications

Damaged cardiomyocytes, necrosis, and cardiogenic shock can result from direct and/or indirect effects of SARS-CoV-2 infection. This can lead to scarring and thinning of the myocardium, myocarditis, cardiomyopathy, arrhythmias, and potentially cardiac arrest.

Eric J. Topol Science 2020;370:408-409

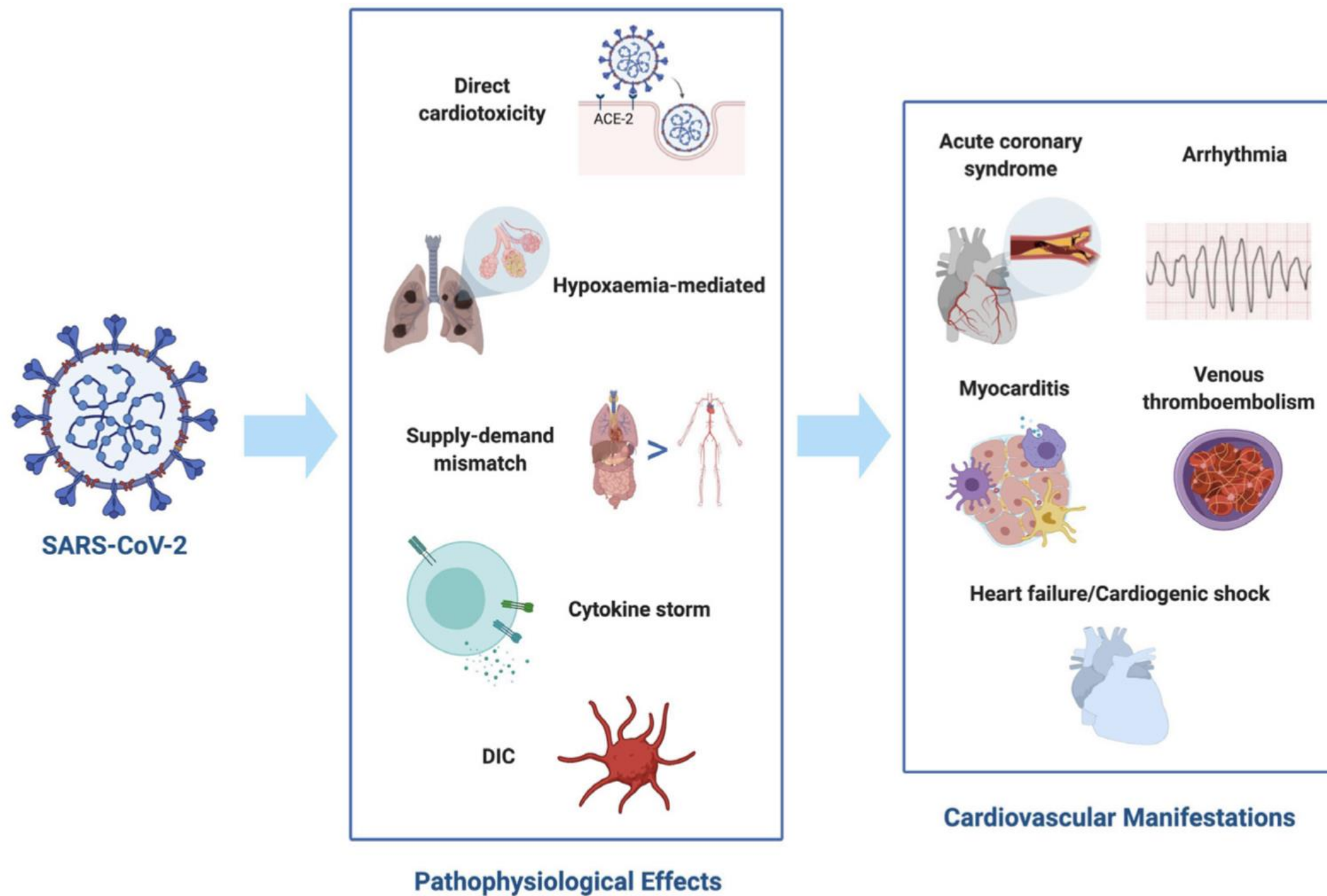
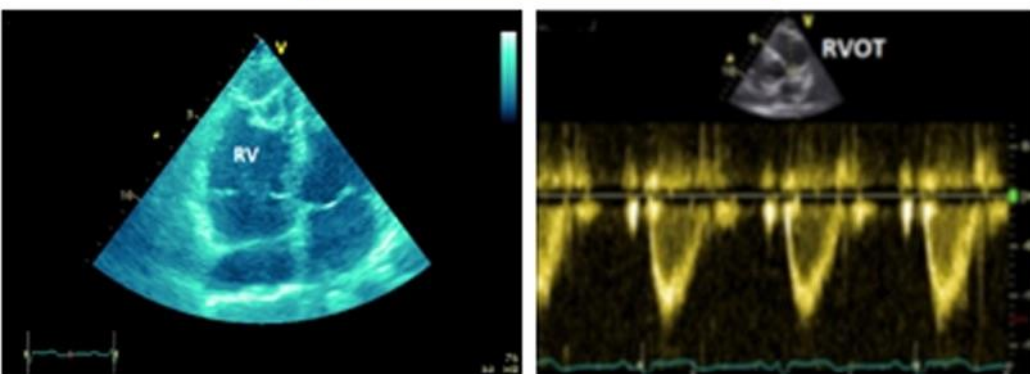
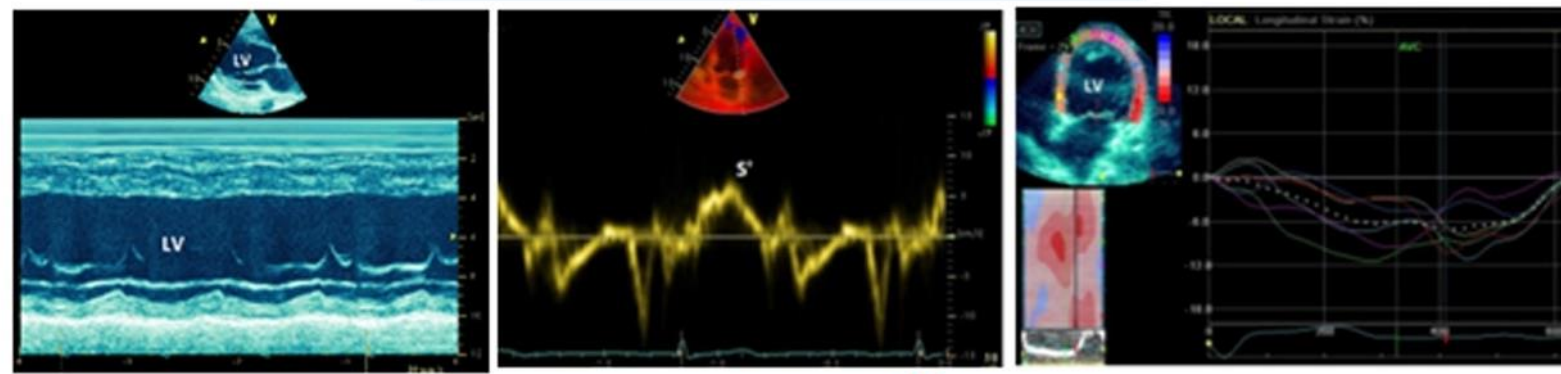


Figure 2 Possible mechanisms of cardiovascular injury due to covid-19. DIC, disseminated intravascular coagulation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

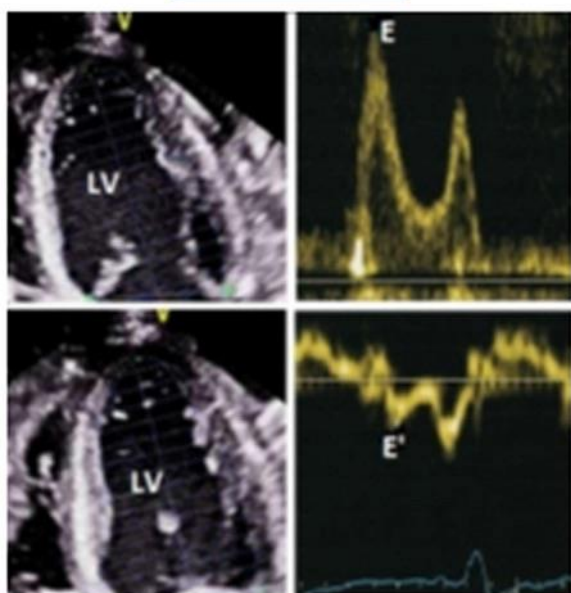
RV dysfunction



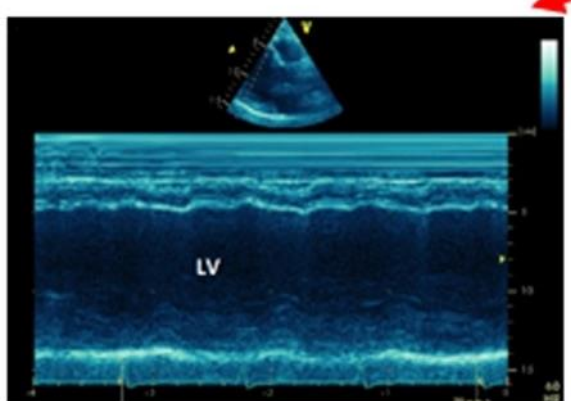
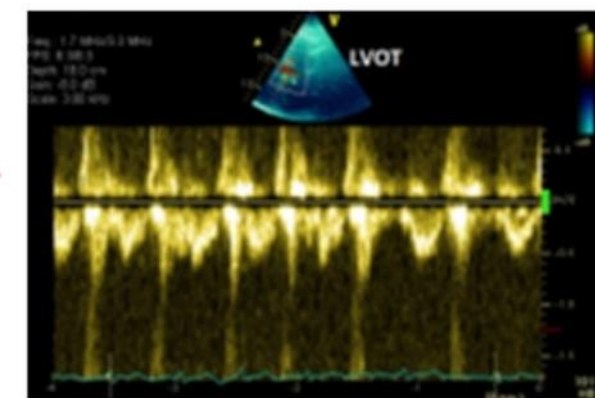
Myocardial injury/HFrEF



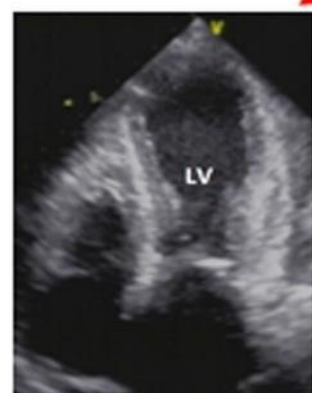
HFpEF



Cardiogenic shock



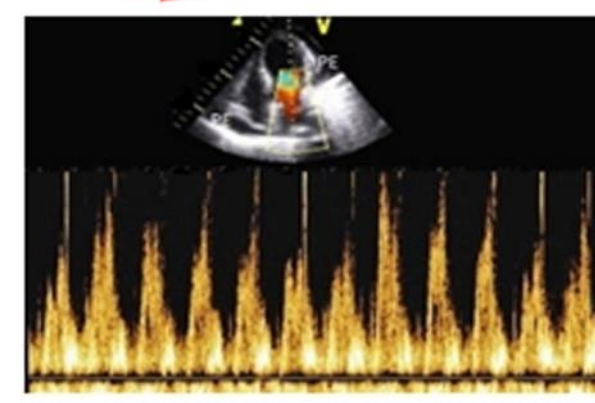
STEMI



Takotsubo



Pericardial effusion



Cardiac tamponade

Table 1 Clinical spectrum of COVID-19 disease^{1 36–41}

Severity of disease	Presentation
Asymptomatic	<ul style="list-style-type: none">▶ No clinical symptoms▶ Positive nasal swab test▶ Normal chest X-ray
Mild illness	<ul style="list-style-type: none">▶ Fever, sore throat, dry cough, malaise and body aches or▶ Nausea, vomiting, abdominal pain, loose stools
Moderate illness	<ul style="list-style-type: none">▶ Symptoms of pneumonia (persistent fever and cough) without hypoxemia▶ Significant lesions on high-resolution CT chest
Severe illness	<ul style="list-style-type: none">▶ Pneumonia with hypoxemia ($\text{SpO}_2 < 92\%$)
Critical state	<ul style="list-style-type: none">▶ Acute respiratory distress syndrome, along with shock, coagulation defects, encephalopathy, heart failure and acute kidney injury

STAY AT HOME. SAVE LIVES.

DO:

- Stay at home, only leaving for the essentials
- Exercise outdoors, practicing social distancing
- Check in on your neighbors, bringing supplies like groceries to those who can't go out

OPEN:

- Grocery and convenience stores
- Pharmacies
- Doctor's offices and hospitals
- Gas stations
- Banks and credit unions
- Takeout & delivery from restaurants
- School lunch program deliveries
- Essential businesses

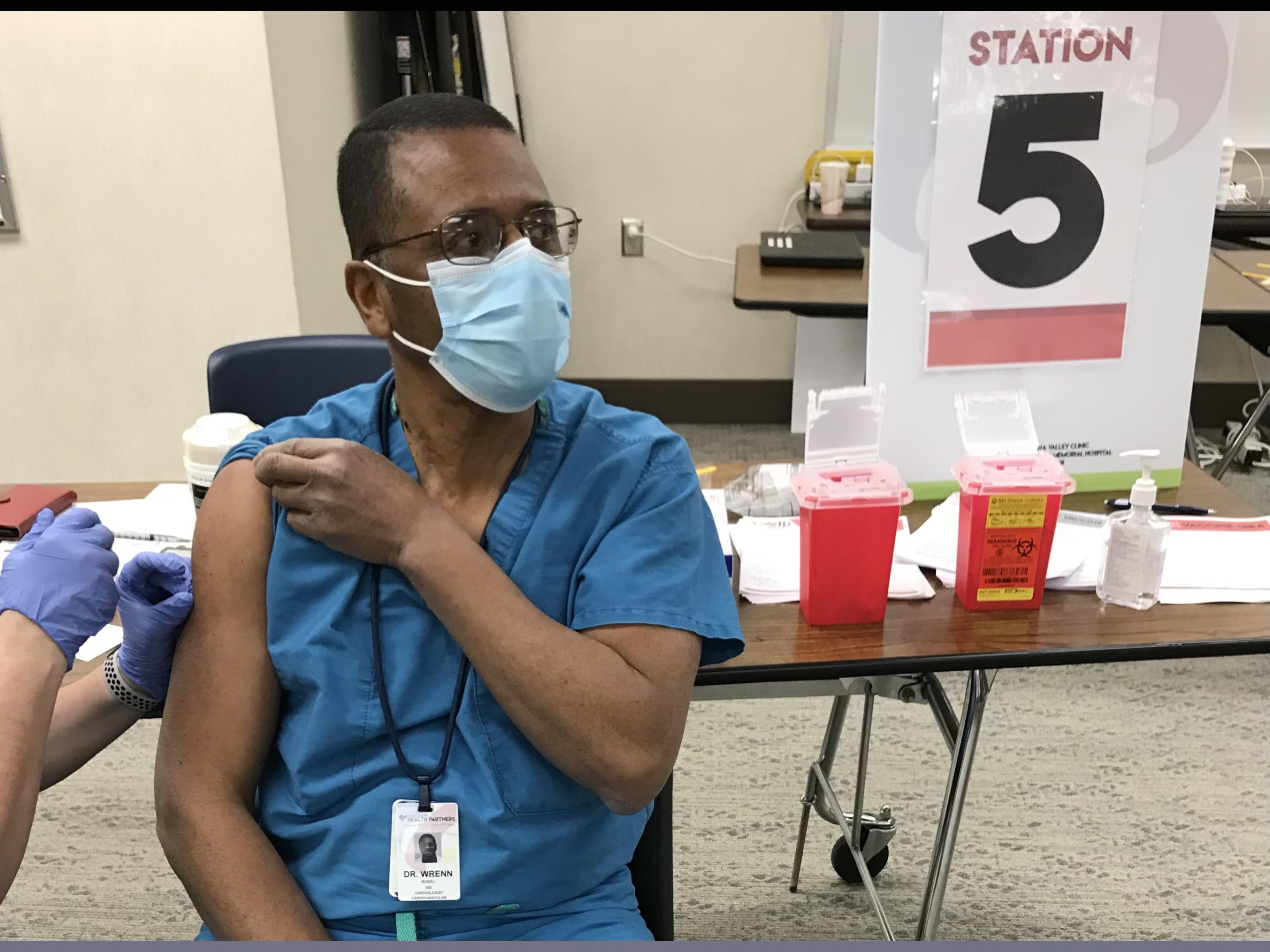
DON'T:

- Gather in large groups or get together with friends
- Have play dates for kids
- Travel unnecessarily
- Stop practicing healthy social distancing

CLOSED:

- Non-essential retail stores and malls
- Barbershops, hair salons, cosmetic stores, and tattoo parlors
- Movie theaters, bowling alleys, and arcades
- Concerts, sporting events, and festivals
- All State beaches along the Seacoast





STATION

5

VALLEY CLINIC
MEMORIAL HOSPITAL

HEALTH PARTNERS
DR. WRENN
MD
CARDIOLOGIST
CARDIOVASCULAR

THANK YOU



QUESTIONS